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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,251	06/06/2002	Keizo Inoue	04853.0089	7644

22852 7590 10/21/2002

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EXAMINER
BERTOGLIO, VALERIE E

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 10/21/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,251	INOUE ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) *18-23,25 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-17 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 14-17 and 24, drawn to a non-human α-tocopherol knockout animal.

Group II, claim(s) 18-23, drawn to a cell lacking expression of α-tocopherol.

Group III, claim(s) 25, drawn to a method of screening medicaments in vivo using a transgenic non-human mammal.

Group IV, claim(s) 25, drawn to a method of screening medicaments in vitro using a transgenic non-human mammalian cell.

Group V, claim(s) 26, drawn to a medicament.

The inventions listed as Groups I-V do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Unity of invention between different categories of inventions will only be found to exist if the specific cominations of inventions are present. Those combinations include:

1) A product and a special process of manufacture of said product.

2) A product and a process of use of said product.

3) A product, a special process of manufacture of said product, and a process of use of said product.

4) A process and an apparatus specially designed to carry out said process.

5) A product, a special process of manufacture of said product, and an apparatus specially designed to carry out said process.

The allowed combinations do not include multiple products, multiple methods of using said products, and methods of making multiple products as claimed in the instant application, see MPEP § 1850. Groups I, III and IV represent different methods requiring different starting products and different method steps to practice the method. Groups I, II, and V represent different products with distinct material compositions and uses.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

During a telephone conversation with Scott Lee on 08 October 2002, a provisional election was made without traverse to prosecute the invention of Group I, claims 14-14 and 24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 18-23, 25, and 26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim

remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim 24 step (a) will be interpreted as "inserting the non-human mammalian embryonic stem cell modified to inhibit the expression of its endogenous gene encoding the α-tocopherol transfer protein gene into an embryo taken from a pregnant female to form a chimeric embryo..." The subject matter of claim 19 should be incorporated into claim 24.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The Brief Description of the Drawings is not properly placed within the specification. The format for the specification, outlined above, does not allow for a section titled "Problems to be solved by the invention" or "Means for solving the Problems" as listed on pages 2 and 3, respectively. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-17 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a knockout mouse whose genome comprises a homozygous disruption in the α-tocopherol protein transfer, such that functional α-tocopherol transfer protein is inhibited, wherein said mouse has a vitamin E deficiency, and a method of making such a mouse using mouse ES cells comprising a targeting vector that disrupts the mouse α-tocopherol protein transfer gene, inserting the cells into

a mouse embryo thereby forming a chimeric embryo, transferring the chimeric embryo into the uterus of a pseudopregnant female, and obtaining a transgenic mouse, does not reasonably provide enablement for any non-human mammal modified to inhibit the expression of its α-tocopherol protein transfer gene produced by using any cell harboring a disruption in the α-tocopherol protein transfer gene as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is directed to a non-human mammal modified to inhibit the expression of its α-tocopherol protein transfer gene and methods of making said transgenic animal.

The state of the art at the time of filing was such that one of skill could not predict the phenotype of transgenics. Leonard (1995, Immunological Reviews, Vol. 148, pages 98-113) disclosed mice with a disruption in the g_c gene which were intended to be a model for X-linked severe combined immunodeficiency (XSCID), but display a variety of unexpected traits (abstract). These knockout mice were expected to have thymocytes with decreased proliferation in response to stimulation with antibodies, but the thymocytes proliferated normally (page 105, line 7). Moens (1993, Development, Vol. 119, pages 485-499) taught two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (page 486, column 1, first full paragraph). Griffiths (1998, Microscopy Research and Technique, Vol. 41, pages 344-358) teach

that despite a known role for the PLP gene based on spontaneous mutations in the gene, the knockout mouse failed to display any of the expected phenotypes (page 350, last paragraph). Thus, the phenotype of knockout mice was unpredictable.

The species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins (1990, Nature, Vol. 344, 541-544) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer (1990, Cell, Vol. 63, 1099-1112) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins, 1989, EMBO J., vol. 8, pages 4065-4072; Taurog, 1988, Jour. Immunol., Vol. 141, pages 4020-4023) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats. Thus, the combination of elements (protein, promoter, species of protein, and species of transgenic) required to obtain a desired effect were not within the realm of routine experimentation at the time of filing.

Not only is the difference in transgenic mice and rats unpredictable for reasons stated above, the art at the time of filing was such that a number of significant limitations regarding the production of non-human transgenic animals existed. Wall (1996,

Theriogenology, Vol. 45, pages 57-68) disclosed the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Overbeek (1994, "Factors affecting transgenic animal production," Transgenic animal technology, pages 96-98) taught that within one litter of transgenic mice, considerable variation in the level of transgene expression occurs between founder animals and causes different phenotypes (page 96, last paragraph). Therefore, it was unpredictable at the time of filing what gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, site of integration, method used and phenotype obtained were required to make a transgenic non-human mammal of interest.

The art at the time of filing further held that targeted gene insertion technology was not available for any species other than mouse. Since homologous recombination is required for gene targeting methods, embryonic stem cell technology must be available to carry out the method. Mullins (1996, J. Clin. Invest., Vol. 98, pages S37-S40) teach that non-mouse ES cells capable of providing germline chimeras were not available (page S38, column 1, first paragraph). Campbell and Wilmut (1997, Theriogenology, vol. 47, pp, 63-72) acknowledge reports of ES-like cells in a number of species, but emphasize that as yet there are no reports of any cells lines that contribute to the germ line in any species other than mouse (page 65). Thus, knockout animals cannot be prepared for any species other than mouse.

The specification does not provide adequate guidance for one of skill in the art to generate non-human transgenic mammals having a disruption in α-tocopherol protein transfer in species other than mice. Homologous recombination requires ES cells and does not occur in somatic cells (Robins, 1981, Cell, Vol. 23, pp. 29-39). Therefore, the methods of gene targeting such as employed in the instant invention require embryonic stem cells. The guidance offered in the specification is limited to the production of knockout mice using mouse ES cells and no teachings or guidance are offered in regard to how one would have prepared any other species of mammal as claimed. The specification and the art at the time of filing fail to disclose any ES cells other than mouse ES cells. Without such guidance, it would have required undue experimentation for one of skill in the art to make any transgenic, non-human mammal.

Applicants fail to enable making and/or using a transgenic having a phenotype other than vitamin E deficiency as broadly encompassed by the claims. The specification teaches a mouse deficient for α-tocopherol protein transfer, displaying a vitamin E deficiency, (pg. 20, lines 14-18, Tables 2 and 3) can be used as a disease model. The claims require a non-human mammal merely having a defective α-tocopherol protein transfer gene and do not require a phenotype. However, the phenotype of the transgenic was unpredictable at the time of filing. The specification does not overcome the unpredictability such that any phenotype could be obtained other than vitamin E deficiency. It would require one of skill in the art at the time the invention was made, undue experimentation to determine how to obtain any phenotype

other than vitamin E deficiency and how to use an animal with any phenotype other than a vitamin E deficiency.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-17 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "artificially" in claim 14 is unclear. "Artificially modified" is not defined in the specification and does not have an art accepted meaning. The term "artificial" is defined as "created to imitate something natural" (http://www.wordsmyth.net/cgi-bin/simplesearch.cgi?matchent=artificial&matchtype=exact&matchid=-1&retall=1).. Use of "artificially" with "modified" does not make sense because it implies that the claimed animal is made to imitate a spontaneous mutation in the α-tocopherol transfer protein gene. However, the mutation disclosed is clearly a disruption that does not occur naturally. The term also does not clearly set forth that the mammal is genetically modified.

The phrase "animal belonging to Rodent" (claims 16 and 17) is unclear. An animal does not belong to a rodent.

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Arai (1998, FASEB Journal, Vol. 12 pp. A658) discloses the isolation of alpha-tocopherol transfer protein and cDNA from liver but does not disclose the amino acid or nucleic acid sequence. Capecchi (1994, Scientific American, March 1994, pages 52-59) disclosed the method of target gene replacement in mice.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is 703-305-5469. The examiner can normally be reached on 7:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1234.

Valarie Bertoglio
Patent Examiner

MICHAEL C. WILSON
PATENT EXAMINER